

Regulatory Oversight of Foreign Clinical Trials: An Examination of the Industry's Influence on FDA Pharmaceutical Regulation and the Implications for Enforcement Activity Both Domestic and Abroad

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ABSTRACT

In recent decades, the pharmaceutical industry has followed the lead of other industries and has globalized its operations. The routine relocation of clinical trials to developing countries has uncovered a jurisdictional gap between domestic regulatory agencies and international mechanisms of governance. This thesis explains why existing regulations governing pharmaceutical clinical trials have created a regulatory vacuum in which ethical clinical practices and consumer safety are undermined. In the case of multinational pharmaceutical companies based in the U.S., I show that existing global protocols do not adequately address the ethical challenges created by the globalization of clinical trials. Meanwhile, the U.S. Food & Drug Administration also suffers from regulatory and supervisory failures due to the ability of the pharmaceutical industry to effectively capture the agency.

INTRODUCTION

In an increasingly globalized world, it has become more and more difficult to enforce health and safety regulations in international commerce. The ever-changing, ever-growing global economy has mitigated the regulatory role of the state, leaving matters of ethical, environmental, and legal compliance to transnational corporations to address at will, unencumbered by

bureaucratic authority. The pharmaceutical industry is one of the many industries that has benefitted from this regulatory void, created by the lack of both global standards and the systematic failures of traditional regulatory bodies to monitor clinical research outside their domestic domains.

The ability to conduct clinical trials overseas allows pharmaceutical companies to circumvent burdensome ethical procedures in favor of cheaper, faster alternatives. Since 2007, twenty of the largest American pharmaceutical companies have based 45% of their reported trials outside the United States.¹ The number of countries serving as trial sites for clinical research has more than doubled in the past decade. There has been widespread and systematic ethical noncompliance on the part of the researchers who do their fieldwork in parts of the developing world, adversely affecting standards of care, quality of informed consent, reasonable availability, transparency of drug trials, and drug interaction effects.²

In this thesis, I will examine why existing regulations governing pharmaceutical clinical trials have created

¹ Seth W. Glickman, et al. "Ethical and Scientific Implications of the Globalization of Clinical Research." *New England Journal of Medicine* 360.8 (2009): 816-23.

² Ezekiel Emanuel, David Wendler, and Christine Grady. "What Makes Clinical Research Ethical?" *JAMA*. 283.20 (2000): 2701-2711.

a regulatory vacuum in which ethical clinical practices and consumer safety are undermined. I will examine how the US Food & Drug Administration responds to the globalization of clinical trials, the influence of the pharmaceutical industry on research regulation, and the factors that contribute to the FDA's regulatory and supervisory failures. The first part of this thesis will briefly outline the nature and ramifications of unethical clinical trials in the developing world. I will then track the historical development of ethical principles guiding human experimentation in order to establish the context upon which modern day research policies are built. Using this foundation, the second part of the thesis will analyze the role of the FDA in monitoring the research activity of the pharmaceutical industry, and the relationship between the evolution of regulatory practices and industry interests. I propose that while the FDA has enormous authority and control over the drug approval and marketing process in the U.S., its efficacy in ensuring that ethical research protocol is followed abroad and that trial data is viable is hampered by industry pressures and inadequate coordination with foreign regulatory agencies.

ETHICAL PROBLEMS IN GLOBAL CLINICAL RESEARCH

A majority of individuals enrolled as research subjects outside of the U.S. live in conditions rife with poverty, disease, limited access to healthcare, and inadequate education. Because they have so few opportunities to pursue their financial and physical security, and generally lack the knowledge and background in healthcare to understand the nature of clinical trials, individuals commonly feel they are in no position to

question or negotiate the terms of their treatments.³ This often leads research subjects to the false assumption that, because the researcher is wearing a lab coat, they are acting in the patient's best interest based on their therapeutic obligation as a physician, when in actuality they are filling the role of a researcher with the primary objective to obtain trial data.⁴ When one Peruvian mother took her sick child to a public hospital in Lima, her son received free treatment, diapers, and meals, and she was urged to sign medical forms even though she could not understand them. Days later, she found out her son had received an experimental therapy. She told a reporter, "Nobody said anything about it being an experiment. I would never have agreed if I had known. I worry all the time."⁵

Researchers often assume that illiterate subjects are incapable of making their own decisions regarding their health, so they dehumanize them and adopt a paternalistic approach, sidestepping the process of obtaining informed consent.⁶ One study showed that 90% of the published clinical trials conducted in China in 2004 did not report ethical review of protocol, and only 18% obtained informed consent.⁷ Another

³ Ibid, 820.

⁴ Ileana Dominguez-Urban. "Harmonization in the Regulation of Pharmaceutical Research and Human Rights: The Need to Think Globally." *Cornell International Law Journal* 30.245 (1997): 245-86.

⁵ Kelly Hearn. "The Rise of Unregulated Drug Trials in South America." *The Nation*, September 21, 2011.

⁶ Diana Crane. "Sociological Perspectives on Research in Human Populations." *Bulletin of the World Health Organization* 55.2 (1977): 91-99.

⁷ Dalu Zhang, et al., "An Assessment of the Quality of Randomized Clinical Trials Conducted in China,"

study demonstrated that when research subjects were given food, money, or shelter in exchange for their participation, they became so reliant on the benefits that withdrawing from the study became unthinkable, even when they were clearly uncomfortable and were legally allowed to opt out at any time.⁸ Financial compensation ultimately takes advantage of most subjects' impoverished living conditions, essentially forcing them to put their own health at risk in the interest of accessing the only medical care or resources available.⁹

In addition to exploiting the disadvantaged position of many research participants, clinical research is disproportionately dedicated to conditions that are only of first world concern. Conditions of global significance — such as malaria, HIV/AIDS, tuberculosis, diarrheal diseases, and lower respiratory infections — cause the majority of premature deaths worldwide.¹⁰ Yet, the majority of research is dedicated to developing treatments for more profitable ailments of affluence — overactive bladder, allergic rhinitis, and acid reflux — which have virtually no prevalence in any other part the world.¹¹ Dr. Jean-Hervé Bradol, President of the

French Section of Médecins Sans Frontières, warned of the dire need to address the gaps between research realities and the global disease burden: “In most cases, [the company’s] objective is not to do research on illnesses affecting poor countries.”¹² Of the 1,556 new drugs developed between 1975 and 2004, only twenty of them targeted the diseases responsible for fifteen million deaths annually. Not even 10% of clinical research focuses on the conditions that cause 90% of deaths worldwide.¹³

Not only is foreign clinical research often exploitative, it can also be scientifically unsound. Because the standard of care in the developing world is usually second-rate and local facilities lack adequate clinical infrastructure, health care professionals, and standard treatments and drugs, many patients who suffer from illnesses are often untreated or undertreated.¹⁴ When these patients participate in a clinical trial, the experimental treatment is being tested on individuals who have had little to no previous exposure to drugs, and thus might have an entirely different effect than it would on a patient who has been medicated, vaccinated, and treated for their entire life, as is common in the first world.¹⁵ These trials do not always take into account how the drug would interact with other treatments that might be administered or present in the bloodstream simultaneously, or the effect of environmental factors.¹⁶ In many cases,

Trials (2008).

⁸ O.O. Ajayi. “Taboos and Clinical Research in West Africa.” *Journal of Medical Ethics* 6 (1980): 61-63.

⁹ Baruch Brody. “Ethical Issues in Clinical Trials in Developing Countries.” *Biomedical Ethics*. By Thomas A. Mappes and David DeGrazia. Boston: McGraw-Hill, 2006 284-88.

¹⁰ World Health Organization. “The top 10 causes of death.” June 2011.
<<http://www.who.int/mediacentre/factsheets/fs310/en/index.html>>

¹¹ Tessa Tan-Torres Edejer. “North-South Research Partnerships: the Ethics of Carrying Out Research in Developing Countries.” *British Medical Journal* 319 (1999): 438-41.

¹² Jean-Hervé Bradol. “Clinical Trials in Africa: Ethical Research Needed on Diseases,” *Doctors Without Borders*, 7 June 2007. Web.

¹³ Ibid.

¹⁴ Glickman, “Ethical and Scientific Implications of the Globalization of Clinical Research,” 819.

¹⁵ Ibid, 820.

¹⁶ FDA Cardiovascular & Renal Drugs Advisory

attention to social ecology and genetic diversity takes a backseat to the convenience of the test subjects' lack of education or poverty. Researchers have found divergence among the genetic profiles of populations according to geographic location; accordingly, some treatments may differ in how they respond to the particular genetic makeup of different people.¹⁷ One study of 42 genetic variants related to pharmacologic response found that more than two-thirds had substantial differences in frequency between persons of African descent and European descent.¹⁸ This has serious implications for trials involving cardiac, circulatory, and neurologic disorders.¹⁹

CASE STUDIES

In order to illustrate the serious implications of the ethical negligence routinely exhibited by pharmaceutical industry sponsors when conducting research, I will describe the clinical development of several controversial treatments.

TROVAN

In 1996, Nigeria experienced the largest epidemic of meningococcal meningitis 20th century Africa had ever seen. Between January and June of that year, 109,580 cases were reported, resulting in more than 11,000 deaths.²⁰ For clinical investigators at the most profitable American pharmaceutical

company, Pfizer, these statistics fell upon eager ears. Earlier that year, Pfizer had developed a potentially lucrative antibiotic called Trovan. Before they could make it available on the market, it had to be approved by the Food and Drug Administration through a process of clinical trials and toxicity testing to demonstrate the efficacy of the treatment.²¹ To nullify concerns that Trovan causes joint damage and other dangerous side effects in children, Pfizer sought to prove its usefulness to the medical community by using it to treat bacterial meningitis. However, there were not enough cases of meningitis in the United States for Pfizer to conduct a statistically significant trial. Upon finding out about the outbreak across the Atlantic, Pfizer promptly opened up an unauthorized clinic in the Nigerian city of Kano.²² Two hundred children were selected from an epidemic hospital; half of them were administered an untested oral dose of Trovan and the other half were given the standard treatment, a dose of intravenous ceftriaxone. None of the patients' parents were told that their children were receiving an experimental and potentially risky drug. Although Trovan proved fatal for eleven children and had detrimental side effects such as deafness, lameness, blindness, brain damage, and paralysis, Pfizer stated in its reports that the death rate was significantly low, and never attempted to conduct follow up examinations on the children to confirm long-term effects of

Committee. 2007 Meeting documents. (www.fda.gov/ohrms/dockets/ac/07/transcripts/2007-4327t-02-part2.pdf)

¹⁷ Glickman, "Ethical and Scientific Implications of the Globalization of Clinical Research," 820.

¹⁸ Ibid.

¹⁹ Ibid, 821.

²⁰ Idris Mohammed, et al., "A severe epidemic of meningococcal meningitis in Nigeria, 1996." *Transactions of the Royal Society of Tropical Medicine and Hygiene* (2000): 265-70.

²¹ "How Drugs Are Developed and Approved." U.S. Food and Drug Administration, 23 Apr. 2010. Web.

²² William DuBois. "New Drug Research, The Extraterritorial Application of FDA Regulations, and the Need for International Cooperation." *Vanderbilt Journal of Transnational Law* 36.161 (2003): 161-207.

the treatment.²³

After FDA approval was obtained in the U.S., Trovan was introduced to the market in February 1998 as an antibiotic with fourteen different uses. That year, Trovan was one of Pfizer's top-selling drugs, bringing in \$160 million and expected to bring in \$1 billion the following year. Within months, reports of liver toxicity in patients with Trovan prescriptions were submitted to the FDA, and the FDA responded by asking Pfizer to include liver toxicity in the list of possible side effects. The next year hundreds of reports of liver problems piled in. By the time the FDA issued a statement recommending that Trovan be used only in hospitals and in rare cases, fourteen patients experienced acute liver failure, and six died.²⁴ As accusations of unethical research practices began to crop up in 2000, Pfizer's researchers were blamed for not obtaining informed consent, keeping inaccurate records, and not explaining to the parents of the test subjects that their children were receiving an experimental and potentially risky drug.²⁵ Despite the clear violations of research ethics, the deceitful exploitation of children during a public health emergency, and the lack of authorization by the Nigerian government, the lawsuit filed against Pfizer was dismissed twice in U.S. Courts, and a Pfizer spokesman stated that the

²³ Ibid, 164.

²⁴ Melody Petersen. "Unforeseen Side Effects Ruined One Blockbuster." *The New York Times*. August 17, 2000.
<<http://www.nytimes.com/2000/08/27/business/unforeseen-side-effects-ruined-one-blockbuster.html>>

²⁵ Anjali Kamat, "WikiLeaks Cables: Pfizer Targeted Nigerian Attorney General to Undermine Suit over Fatal Drug Tests," *Democracy Now*, 17 Dec. 2010. Web.

trials were "sound from medical, scientific, regulatory and ethical standpoints."²⁶

SYNFLORIX

Between 2007 and 2008, GlaxoSmithKline (GSK) conducted a trial in rural areas of Argentina, Colombia, and Panama on approximately 24,000 children between the ages of 6 and 16 weeks to study the efficacy of a pneumococcal vaccine, Synflorix.²⁷ This vaccine was developed to prevent both pneumococcal diseases, which includes meningitis, sepsis, pneumonia, and otitis media, as well as bacterial respiratory infections.²⁸ Most of the parents of trial subjects were under-age, illiterate, or did not understand the implications of the treatment received. "They are vulnerable sections of society," Jorge Yabkowsky, president of the Argentine Federation of Health Professionals, explained, "They were unable to read any kind of consent form."²⁹ Researchers received \$350 from GSK for each subject they enrolled.³⁰ Fourteen babies who were randomly assigned to the placebo group died during the trial.³¹ In 2011, Argentinian courts

²⁶ "Nigeria sues drugs giant Pfizer." *BBC News*, 5 June 2007.

²⁷ Andrea Gerlin. "Glaxo to Appeal Fines in Argentina Case Over Synflorix Trial." *Bloomberg*. January 3, 2012.
<<http://www.bloomberg.com/news/2012-01-03/glaxo-to-appeal-fines-in-argentina-case-over-synflorix-trial.html>>

²⁸ "Glaxo may not launch Synflorix vaccine in U.S." *Reuters*. February 5, 2009.
<<http://www.reuters.com/article/2009/02/05/glaxo-synflorix-idUSL577085220090205>>

²⁹ "GlaxoSmithKline fined over trials on the babies of Argentinian poor." *The Telegraph*, 11 January 2012.

³⁰ Ibid.

³¹ Natalie Fuertes. "World Report: GSK malpractice case raises questions about trial standards." *The Lancet*. 379 (2012): 508.
<<http://www.iapcoi.com/hp/pdf/GSK%20malpra>>

sued GSK \$92,000 for “administrative irregularities” in obtaining informed consent. GSK is currently in the process of appealing the decision, claiming they “[conduct] clinical trials to the same high standards irrespective of where in the world they are run.”

KETEK

In the 1990s, French company Aventis Pharmaceuticals (later Sanofi-Aventis) began conducting clinical trials of a new antibiotic, Ketek (telithromycin), developed to treat bacterial respiratory infections such as sinusitis, bronchitis, and pneumonia.³² Most of the trials were done in Hungary, Morocco, Tunisia, and Turkey.³³ Several weeks before FDA approval of Ketek, an American researcher who had enrolled more than 400 subjects in one of Ketek’s key clinical trials was sentenced to 57 months in prison for fabricating 91% of her trial data.³⁴ It was later revealed that she collected \$400 from Aventis for every subject she enrolled. Even after her sentencing, the FDA approved Ketek as safe in 2004, primarily based on foreign clinical data, and it was introduced to the market.³⁵

By 2006, the FDA received fourteen reports of liver failure, 23 reports of serious liver injury, and numerous other reports of liver damage,

including four deaths.³⁶ A study done that same year examined three previously healthy patients who had taken Telithromycin. Within days, all three of the patients had acute hepatitis, jaundice, and “markedly abnormal results on liver function tests.”³⁷ One of the patients recovered, one needed orthotropic liver transplantation, and the third died. Further examination of the second and third patients revealed “massive hepatic necrosis,” or the premature death of cells in living tissue.³⁸ Dr. David Graham wrote an email in 2006, obtained by the *New York Times*, revealing he thought approving Ketek was a mistake and strongly advised its withdrawal. He explained, “We don’t really know if the drug works; no one is claiming it works better than other, safer drugs; and we’re flying blind as far as safety goes, except for our own A.D.R. data that suggests telithromycin is uniquely more toxic than most other drugs.”³⁹ He went on to write, “For FDA to refer to its being assured by post-marketing data from Latin America and Europe as a basis for declaring ‘Ketek is safe’ is in my opinion a great abuse of such surveillance data.” Several weeks after these emails were made public, the FDA added to Ketek’s warning section to include adverse events such as “visual disturbances, loss of consciousness, and hepatic toxicity.”⁴⁰

ctice%20case%20raises%20questions%20about
%20trial%20standards.pdf>

³² KD Clay, JS Hanson, SD Pope, RW Rissmiller, et al. “Brief communication: severe hepatotoxicity of telithromycin: three case reports and literature review.” *Annals of Internal Medicine* 144.6 (2006): 415-20.

<<http://www.ncbi.nlm.nih.gov/pubmed/1648145>
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³³ Donald L. Barlett and James B. Steele. “Deadly Medicine.” *Vanity Fair*, January 2011.

³⁴ Hearn, “The Rise of Unregulated Drug Trials in South America.”

³⁵ Ibid.

³⁶ Gardiner Harris. “Approval of Antibiotic Worried Safety Officials.” *The New York Times*. 2006. <

http://www.nytimes.com/2006/07/19/health/19fda.html?_r=1>

³⁷ Clay, “Brief communication.”

³⁸ Ibid.

³⁹ Harris, “Approval of Antibiotic Worried Safety Officials.”

⁴⁰ Food & Drug Administration. “FDA Announces Label and Indication Changes for the Antibiotic Ketek.” February 12, 2007.

<<http://www.fda.gov/NewsEvents/Newsroom/Pr>

It was not until February 2007, when more than 5 million Ketek prescriptions had been written, that the FDA announced that Sanofi-Aventis had to include a black box warning with the medication, as well as a Patient Medication Guide, and restrict its use for two previously approved conditions – acute bacterial sinusitis and acute bacterial bronchitis.⁴¹ For these conditions, the FDA concluded that the risks of Ketek greatly outweighed the potential benefits. Iowan Senator Charles Grassley, a chairman of the Finance Committee who was involved in investigating Ketek, said, “It’s no surprise to learn that the F.D.A. didn’t listen to Dr. Graham on the dangers of Ketek. The F.D.A. has made it their business to discredit Dr. Graham and others who aren’t willing to cater to the drug companies.”⁴²

DEVELOPMENT OF GLOBAL STANDARDS

In the past century, international efforts have been made to develop global standards of conduct for human experimentation. Current regulations for clinical research are derived from a series of international documents that form the foundation of research ethics. In this section, I will outline the historical contexts, important contributions, and fundamental gaps of each of these international documents to demonstrate why they fail to complement national regulations by reigning in the pharmaceutical industry on a global scale.

[essAnnouncements/2007/ucm108842.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=ketek&utm_content=2](http://www.fda.gov/oc/2007/ucm108842.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=ketek&utm_content=2)

⁴¹ Ibid.

⁴² Harris, “Approval of Antibiotic Worried Safety Officials.”

Before World War II, no universal ethical document existed to guide research involving humans. When Allied troops moved to liberate Nazi concentration camps, they were horrified to discover that scores of prisoners had been subjected to ghastly medical experiments, carried out by Nazi researchers in an attempt to test the limits of the human body, develop weapons of warfare, and test experimental antibiotics. None of the prisoners gave consent or willingly volunteered to be exposed to diseases such as malaria, jaundice, and typhus, or to be operated on in a variety of dangerous surgical procedures.⁴³

The subsequent Doctors’ Trial (United States of America v. Karl Brandt, et al.), the first of twelve trials for war crimes held by American authorities before American military courts in Nuremberg between October 1946 and August 1947, illuminated the dire need for an international consensus on bioethics.⁴⁴ Of the twenty-three defendants, twenty were medical doctors charged with crimes against humanity, such as performing medical experiments without the subjects’ consent on prisoners of war and civilians of occupied countries.⁴⁵ Sixteen of the accused were

⁴³ Matthew Lippman. “The Nazi Doctors Trial and the International Prohibition on Medical Involvement in Torture.” *Loyola of Los Angeles International and Comparative Law Journal* 15.2 (1993): 395-441.

⁴⁴ United States of America vs. Karl Brandt, et al. 1946.

⁴⁵ Opening Statement of the Prosecution by Brigadier General Teleford Taylor, 9 December 1946.
<<http://www.mazal.org/archive/nmt/01/NMT01-T027.htm>>

indicted and sentenced to execution or imprisonment, despite their protests that there was no law that differentiated between legal and illegal human experiments.⁴⁶ In response, Dr. Leo Alexander, an American physician and medical advisor to the trials, proposed a set of principles to define legitimate and ethical medical research. Four more principles were added and adopted by the trial verdict, creating the Nuremberg Code.

This code was the first established set of ethical principles for research involving human beings and prompted international dialogue regarding the development of international standards for research on humans. It emphasized, above all, informed and voluntary consent, as well as the absence of physical and mental suffering of the patient, an analysis of risks and benefits, scientific validity, and beneficence of the researcher with regards to the subject.⁴⁷ However, as the interest in medical research and advancement of new research methods grew, the need for more developed guidelines grew as well. Physician-researchers found that the Nuremberg Code was too stringent and inflexible and hindered their research. It made no provisions or guidelines dealing with children or the mentally impaired as research subjects and overemphasized

⁴⁶ Federal Research Division. Library of Congress. "Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law." October 1946 - April 1949. <http://www.loc.gov/rr/frd/Military_Law/NTs_war-criminals.html>

⁴⁷ Ibid.

informed consent.⁴⁸

In 1964, the World Medical Association presented the Declaration of Helsinki. Rather than a list of uncompromising principles, the Declaration was intended to be a more versatile ethical model, which would serve as guidelines for physicians. American researcher Henry Beecher explained: "The Nuremberg Code presents a rigid act of legalistic demands... The Declaration of Helsinki on the other hand, presents a set of guides. It is an ethical as opposed to a legalistic document and is thus more broadly useful than the one formulated at Nuremberg."⁴⁹ The President of the Council for International Organizations of Medical Sciences (CIOMS) stated that the Declaration of Helsinki improved upon the Nuremberg Code's "circumstantial" guidelines by placing them "more correctly in the context of generally accepted medical traditions."⁵⁰

The Declaration accomplished this versatility by isolating therapeutic and non-therapeutic, or scientific, research.⁵¹

⁴⁸ George J. Annas. "The Changing Landscape of Human Experimentation: Nuremberg, Helsinki, and beyond." *Journal of Law and Medicine* 92.2 (1992): 119. <<http://connection.ebscohost.com/c/articles/9609042703/changing-landscape-human-experimentation-nuremberg-helsinki-beyond>>

⁴⁹ Quoted in W. Refshauge, *The Place for International Standards in Conducting Research for Humans*, 55 Bull. World Health Org. 133-35 (Supp. 1977)

⁵⁰ Refshauge, *supra* note 5, at 137.

⁵¹ Annas, "The Changing Landscape of Human Experimentation: Nuremberg, Helsinki, and beyond."

While therapeutic research is utilized strictly for the benefit of the patient, scientific research is done to acquire scientific data. The patient's consent is valued differently according to which type of research they are exposed: if it is therapeutic, the physician may make decisions for the patient without their consent, assuming that the physician has the patient's best interests in mind. It was thought that acquiring consent in these instances would be too cumbersome and would create unnecessary difficulty in caring for the patient.⁵² If the patient is involved in scientific research, their complete informed consent is absolutely necessary because there may be no direct benefit to the patient at all.⁵³ But when it comes to types of research like drug trials, they may be difficult to label as strictly therapeutic or scientific. Experimental treatments may be given in a therapeutic treatment, but they may not be proven to be safe or effective and are therefore not expected to necessarily benefit the patient.⁵⁴ In the 1975 revision, another provision was added, pushing for formal peer review of research protocols, which would give institutional review boards the responsibility to consider and comment on proposed experimental procedures.⁵⁵

During the 1990s, a series of trials were conducted in developing countries that incited international controversy and illustrated serious deficiencies in the

newly revised global standards. In 1994, trials were conducted in Uganda to determine if zidovudine (AZT), an antiretroviral drug, would decrease the likelihood of mother-to-child transmission of HIV. Researchers found that administering the drug during pregnancy and labor reduced transmission to infants by two-thirds, and that it had the potential to save one out of every seven infants born to HIV-positive women.⁵⁶ These studies proved to be controversial because a number of study participants were randomly assigned to placebo control groups. Although the use of placebos allows for quicker and more accurate results than equivalency studies, which are done to determine efficacy of a treatment in comparison to a pre-established level of efficacy, it deprives those unfortunate enough to be randomized into the control group of any kind of treatment, even if one exists.⁵⁷ Placebo-controlled studies were justified because research subjects were not being denied a treatment they would have otherwise received. This logic proved to be problematic because it created an incentive for researchers to conduct studies in parts of the world with the least access to medical care, where locals would more willingly risk being put into the placebo group out of desperation for

⁵² Dawn Joyce Miller. "Research and Accountability: The Need for Uniform Regulation of International Pharmaceutical Drug Testing." *Pace International Law Review* 13 (2001): 204.

⁵³ *Ibid*, 204.

⁵⁴ *Ibid*, 204.

⁵⁵ Annas, "The Changing Landscape of Human Experimentation: Nuremberg, Helsinki, and beyond."

⁵⁶ Peter Lurie, Sidney M. Wolfe. "Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries." *New England Journal of Medicine* 337 (1997): 853-856.

<<http://www.nejm.org/doi/full/10.1056/NEJM199709183371212>>

⁵⁷ Brooks Jackson, et al. "Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda." *The Lancet* 362 (2003): 859-868.

<[http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(03\)14341-3/abstract](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(03)14341-3/abstract)>

even a 50% chance of receiving treatment.

Following these incidents, the Declaration's revisions in 2000 contained a provision that stated, "A new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods," and that a placebo (no treatment) is acceptable only in cases where no proven method exists.⁵⁸ Another provision stated that all study participants, on the completion of a clinical trial, must be provided with the "best proven diagnostic and therapeutic methods."⁵⁹ Before the codification of this principle, most research participants in the developing world were not provided with the proven treatment after the conclusion of the study, while participants in wealthy countries were supplied with the proven treatment until their death or the end of their illness. Although these provisions were well intentioned, they failed to fully address the root problems. The banning of placebos or experimental treatments when a proven treatment already exists is meant to promote a global standard of care, granting every trial subject the same treatment they would have received anywhere else in the world. This principle does not consider the extremely high cost, sophisticated equipment, and advanced medical training that is necessary to provide many standard treatments or perform standard procedures. Thus, it effectively bans the development of more practical treatments that would be cheaper and easier to implement or administer in the less advanced

⁵⁸ World Medical Association. "Declaration of Helsinki: ethical principles for medical research involving human subjects." *Journal of Postgraduate Medicine* 48.206 (2002).

⁵⁹ Dismantling the Helsinki Declaration 30, 2003.

healthcare systems of developing countries.⁶⁰

In 1949, the World Health Organization (WHO) and the United Nations Educational, Scientific and Cultural Organization (UNESCO) founded the Council of International Organizations of Medical Sciences (CIOMS), an international non-governmental organization designated to maintain "collaborative relations" with the UN, UNESCO, and WHO. In the late 1970s, CIOMS and WHO teamed up to establish bioethics as an integral part of medical research. They sought to develop an ethical framework "to indicate how the ethical principles that should guide the conduct of biomedical research involving human subjects, as set forth in the Declaration of Helsinki, could be effectively applied, particularly in developing countries, given their socioeconomic circumstances, laws and regulations, and executive and administrative arrangements."⁶¹ In 1982, WHO and CIOMS published *International Ethical Guidelines for Biomedical Research Involving Human Subjects*.

The document is intended to guide research that involves human subjects, which includes "studies of a physiological, biochemical or pathological process; the response to a specific intervention... in healthy subjects or patients; controlled trials of diagnostic preventative, or

⁶⁰ David Wendler and EJ Emanuel. "The Standard of Care Debate: Can Research in Developing Countries be Both Ethical and Responsive to Those Countries' Health needs?" *American Journal of Public Health* 94.6 (2004): 923-928.

⁶¹ Council for International Organizations of Medical Sciences in collaboration with the World Health Organization. "International Ethical Guidelines for Biomedical Research Involving Human Subjects." Geneva, 2002.

therapeutic measures; studies designed to determine the consequences of specific preventative or therapeutic measures; studies concerning health-related behavior”.⁶² The guidelines call for research to adhere to basic principles: 1) respect for persons: respect for autonomy and protection of those with impaired autonomy; 2) beneficence: the obligation to maximize benefit and minimize harm; 3) justice: the treatment of each individual subject with the utmost respect and dignity, the equal distribution of burdens and benefits between those involved in the research, and sensitivity to the specific needs of subjects.⁶³ Research protocol should clearly elucidate “the aim of the research; the reasons for proposing that it involve human subjects; the nature and degree of any known risks to the subjects; the sources from which it is proposed to recruit subjects; and the means proposed for ensuring that subjects’ consent will be adequately informed and voluntary”, and the protocol should be scientifically and ethically reviewed by independent investigative bodies.⁶⁴

However, due to the spread of HIV/AIDS, biotechnological advancements, and new research practices, CIOMS was obligated to publish two revisions: *International Guidelines for Ethical Review of Epidemiological Studies* (1991), and *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (1993). Ethical issues that arose after 1993 exposed gaps in the revisions that were connected to clinical trials done in developing countries. Some argued for local decision-

making, the avoidance of paternalism, and the development of low-cost public health solutions in communities where research was done. After much deliberation and re-drafting, CIOMS published the latest revision in 2002, which is comprised of general ethical principles and twenty-one guidelines. Just like the first draft, the current document is intended “to be of use, particularly to low-resource countries, in defining national policies on the ethics of biomedical research, applying ethical standards in local circumstances, and establishing or redefining adequate mechanisms for ethical review of research involving human subjects.”

The actual guidelines and their respective detailed commentaries consist of rules such as ethical justification and scientific validity of biomedical research involving human beings, ethical review committees, ethical review of externally sponsored research in the country sponsoring the research, individual informed consent, obligations of sponsors and investigators, benefits and risks of study participation, choice of control treatment, equitable distribution of risks and benefits, research on children, right of injured subjects to treatment and compensation, and more.⁶⁵

At the 2001 Conference on Ethical Aspects of Research in Developing Countries, participants compiled a set of developed criticisms of the CIOMS guidelines. In particular, they focused on the idea of reasonable availability, explained in Guideline 10: “The sponsor and investigator must make every effort to ensure that: 1) the research is responsive to the health needs and the

⁶² Ibid, 19.

⁶³ Ibid, 18.

⁶⁴ Ibid, 18.

⁶⁵ Ibid, 25-82.

priorities of the population or community in which it is to be carried out; and 2) any intervention or product developed or knowledge generated, will be made reasonably available for the benefit of that population or community.”⁶⁶ This guideline was criticized because of its reliance on a “mistaken conception” of exploitation – it focuses on the products of the research rather than the level of benefit.⁶⁷ While benefits are provided (i.e. “the fruits of the research”), they may not be necessarily fair or appropriate for the community.⁶⁸

Reasonable availability not only “embodies a very narrow notion of benefits,” it makes the benefit reliant upon the success of the clinical trial, ignoring other potential benefits such as “the training of health care or research personnel, the construction of health care facilities and other physical infrastructure, and the provision of public health measures and services beyond those required by the research trial.”⁶⁹ Furthermore, it is not applicable to Phase I and II drug and vaccine testing, or to genetic, epidemiology, and natural history research.⁷⁰ The Conference ultimately contributed a few constructive recommendations, including “providing collateral health services unnecessary for the research itself; public health measures for the country or community; long-term research collaboration; and sharing of financial rewards from research results, including intellectual

property rights”, as well as advocate for transparency of the research process, extensive deliberative dialogue with the subject community, and a publicly available record of research protocol and benefit agreements.⁷¹

Existing international guidelines have had a global impact. The Nuremberg Code set the precedent for an internationally accepted set of bioethical principles to guide human experimentation. The Declaration of Helsinki has been characterized as the “cornerstone of biomedical research for the past 30 years” and the indisputable foundation for ethical decision-making in research.⁷² The CIOMS guidelines proposed suggestions for the application of ethical principles specifically for research conducted in developing countries. Although none of these ethical guidelines are legally binding under international law, they have in some part influenced or been integrated into numerous international, regional, and national legislation on human experimentation.⁷³ The Code of Federal Regulations, consisting of guidelines directing federally funded research in the U.S., is partly based on the Nuremberg Code.⁷⁴ In 1981, the U.S. Courts cited the Nuremberg Code when stating, “The

⁶⁶ Ibid, 51.

⁶⁷ 2001 Conference on Ethical Aspects of Research in Developing Countries. “Moral Standards for Research in Developing Countries.” Hastings Center Report. (2004): 17.

⁶⁸ Ibid, 19.

⁶⁹ Ibid, 21.

⁷⁰ Ibid, 21.

⁷¹ Ruth Macklin. *Double Standards in Medical Research in Developing Countries*. Cambridge University Press. (2004): 152.

⁷² Francis Crawley & Joseph Hoet. *Ethics and Law: The Declaration of Helsinki Under Discussion*. 150 Bulletin of Medical Ethics 9.10: (1999).

⁷³ Delon Human and Sev S. Fluss. “The World Medical Association’s Declaration of Helsinki: Historical and Contemporary Perspectives.” 2001. <http://www.wma.net/en/20activities/10ethics/10helsinki/draft_historical_contemporary_perspectives.pdf>

⁷⁴ Protection of Human Subjects, 45 C.F.R. § 46 (2009).

international consensus against involuntary human experimentation is clear.”⁷⁵ The Belmont Report, the foundation of the Food & Drug Administration’s duties and functions, is based on the Declaration of Helsinki. While all have been widely accepted and recognized worldwide, they have been criticized for being devised in reaction to particular events, such as the Nazi experiments or the Tuskegee and Willowbrook scandals.^{76,77,78} As a result, they inadequately or unevenly address certain principles according to the context of the document’s conception: the Nuremberg Code relies too much on informed consent, while the Declaration is too ambiguous to allow for pragmatic application, and CIOMS does not fully address the needs of research participants from the developing world. Furthermore, the guidelines are almost entirely oriented towards the “integrity and judgment” of the researcher, and have no real methods of enforcement.⁷⁹

⁷⁵ United States v. Jaffe, 663 F.2d 1226
<<http://law.justia.com/cases/federal/appellate-courts/F2/663/1226/147056/>>

⁷⁶ Emanuel, “What Makes Clinical Research Ethical?” 2702.

⁷⁷ The Tuskegee syphilis experiment was a 40-year-long study conducted by the Public Health Service to observe and record the progression of syphilis in African American men, who were never informed of the real purpose of the study and were deprived of effective treatment, penicillin, even when it became available in 1947. See “The Tuskegee Timeline,” Centers for Disease Control and Prevention. 2011.

⁷⁸ Between 1956 and 1970, students housed at Willowbrook State School, a government-funded school for children with intellectual disabilities, were intentionally infected with the hepatitis virus in order to help researchers develop a vaccine. See *Medical Ethics and Humanities* by Frederick Paola, et al. (Jones & Bartlett Learning, 2010). Pages 285-286.

⁷⁹ Dominguez-Urban, “Harmonization in the

The inability of global standards to act as effective regulatory mechanisms for foreign clinical trials place the burden of supervision on states.

THE ROLE OF THE FDA

In 1938, U.S. Congress passed the Food, Drug, and Cosmetic Act (FDCA).⁸⁰ This law gave the Food and Drug Administration the responsibility to guarantee: the safety and efficacy of human and veterinary drugs and medical devices, safety and proper labeling of food and cosmetics, and protection of public health from electronic product radiation.⁸¹ The FDA is mandated to protect public health through product regulation and supervision. The FDCA endows the FDA with the authority to inspect and approve new drugs and medical devices before they may be made available to the public, including the clinical trials required to develop them, as well as the duty to promptly withdraw a product if it proves to be unsafe after being introduced to the market. FDA restrictions apply to: research involving human subjects that is conducted, funded, or bound to regulation by any federal agency, as well as research conducted, funded, or bound to regulation by the federal government outside the U.S.⁸² Research that is not conducted or funded by the federal government, but subject to federal regulations, is required to be evaluated and given approval by an institutional review board according to

Regulation of Pharmaceutical Research and Human Rights: The Need to Think Globally,” 274.

⁸⁰ Federal Food, Drug, and Cosmetic Act of 1938, 21 U.S.C. Chapter 9.

⁸¹ Food and Drug Administration, 21 U.S.C. § 393(b)(2009).

⁸² Protection of Human Subjects, 45 C.F.R. §46.101 (2009).

the same regulations.⁸³ Because all drugs must be approved by the FDA before being introduced into U.S. markets, any pharmaceutical corporations that conduct clinical trials to develop drugs to sell in the U.S. fall under the umbrella of restrictions as put forth by the Code of Federal Regulations.

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, established after the Tuskegee Syphilis scandal, was Congressionally mandated in 1974 to investigate all federally sponsored human subject research and review ethical research principles. The most prominent of their published reports is the Belmont Report, which is based on the Declaration of Helsinki and focused on three basic principles – respect for persons, beneficence, and justice – which were then applied to modern FDA research regulations.^{84,85}

“Respect for persons” is actualized through the rule of informed consent. The FDA requires that research may be done only under the condition that “the legally effective informed consent of the subject or the subject’s legally authorized representative” is obtained.⁸⁶ Informed consent is defined as disclosing to the patient information regarding the study’s purposes and methodology, potential

risks and intended benefits, other alternative treatments, and the patient’s right to withdraw from the study at any time, presented in a way the patient can understand.⁸⁷ The patient may not be coerced in any way. Informed consent may be bypassed only if the physician demonstrates that the patient was in a life threatening situation, the patient was unable to give consent, there was no time to obtain consent from another legitimate source, and there are no alternative treatments available.⁸⁸

“Beneficence” involves respecting the integrity and autonomy of the individual, as well as promoting their well being and protecting them from harm. This principle is the basis of the researcher’s obligation to maximize benefits and minimize harm to the study participants. A clinical trial may only be conducted if it is supported by a positive risk/benefit analysis and the subject is not exposed to an unreasonable level of risk. “Justice” involves the equitable distribution of research benefits and burdens, and calls for a fair and appropriate method of selecting research subjects. This principle gives rise to the researcher’s responsibility to select research populations based on the relevance of the study to their specific conditions, and to avoid taking advantage of economic, social, racial, or sexual vulnerabilities.

These three principles are fulfilled by research protocol inspection by institutional review boards (IRB). IRBs, also called independent ethics committees or ethical review boards, are

⁸³ Ibid.

⁸⁴ David Perlman. “Ethics in Clinical Research: A History of Human Subject Protections and Practical Implementation of Ethical Standards.” Temple University School of Pharmacy. 2004. <http://www.socra.org/pdf/200405_Ethics_Clinical_Research_History.pdf>

⁸⁵

<http://www.hhs.gov/ohrp/policy/belmont.html#xbenefit>

⁸⁶ General Requirements for Informed Consent, 21 C.F.R. § 50.20 (1999).

⁸⁷ Elements of Informed Consent, 21 C.F.R. § 50.25 (2011).

⁸⁸ Exception from General Requirements, 21 C.F.R. § 50.23 (2011).

committees officially assigned by the FDA to review biomedical research proposals, approve, disapprove, or require modification of research protocol, and monitor clinical trials involving humans. IRBs provide, in theory, broad protection of the health and safety of clinical research subjects. In order to approve research proposals, IRBs must ensure: (1) risks to subjects are minimized by using viable research design; (2) anticipated benefits reasonably outweigh risks to subjects; (3) choice of research subject population is justified and valid, and vulnerable populations are not being taken advantage of; (4) informed consent will be obtained; (5) informed consent will be officially documented; (6) data collection monitoring techniques will ensure the safety of research subjects, and (7) subject privacy is ensured and data is kept confidential.⁸⁹ Furthermore, additional precautionary measures will be taken to ensure ethical research protocol if the research population is “vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.”⁹⁰

When clinical research was still done primarily in the U.S., these regulations for the most part effectively protected trial subjects, ensured the scientific validity of research protocol, and verified the accuracy of trial data.⁹¹ But as sponsors began to submit foreign trial data, the FDA had to scramble to adapt methods of supervision. The FDA

gives sponsors conducting clinical trials abroad two options. First, they may submit an Investigational New Drug Application (IND) and be supervised by an IRB, just as they would be required to if the research were conducted in the U.S. An IND must contain pharmacological and chemical information about the drug, the objectives and duration of the clinical trial, background information on previous human and animal testing, foreign investigational or marketing experience, and manufacturing information.⁹² It must also include a comprehensive outline for the clinical investigation, detailing the motivation behind the study, the components being studied, names and qualifications of all clinical investigators, research methodology, detailed protocols and procedures, the number of subjects to be enrolled, any anticipated risks and side effects, and information on the drug’s safety and effectiveness based on previous studies.⁹³

The second option is the most commonly used – the clinical trials must be done in accordance with the Declaration of Helsinki, or the regulations of the host country, whichever provides more extensive protections of the research subjects.⁹⁴ If host country guidelines are used, the clinical investigator must explain the differences between the standards used and those put forth by the Declaration of Helsinki, and their reasoning in choosing those guidelines. To gain premarket approval based only on foreign clinical data requires that the data is relevant to U.S. markets and medical practices, the

⁸⁹ Criteria for IRB Approval of Research, 21 C.F.R. § 56.111 (2001).

⁹⁰ *Ibid.*

⁹¹ Dominguez-Urban, “Harmonization in the Regulation of Pharmaceutical Research and Human Rights: The Need to Think Globally.”

⁹² Investigational New Drug Application, 21 § 312.23 (2002).

⁹³ *Ibid.*

⁹⁴ Research conducted outside the United States, 21 C.F.R. § 814.15 (1986).

clinical investigators are competent, and the understanding that the FDA may conduct on-site inspections if deemed necessary.⁹⁵ However, the FDA is often not aware that a clinical trial is being conducted abroad until the drug application is being submitted for market approval, after the completion of research, preventing field inspectors from supervising trial sites.⁹⁶ Foreign regulatory bodies may also monitor and inspect trials, but they are not obligated to share information or collaborate with the FDA.⁹⁷

The FDA is responsible for ensuring that these regulations are followed and is allowed to cooperate with foreign governments and agencies to “reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements.”⁹⁸ While this does not explicitly imply extraterritorial jurisdiction, it certainly necessitates some amount of inspection to ensure the validity of the scientific data that will be used to determine the safety and efficacy of that drug. In 1990, only 271 clinical trials were conducted abroad to develop drugs for American markets. But by 2008, the number of foreign trials escalated 2,000%, to 6,485.⁹⁹ That same year, 80% of approved marketing applications for new drugs involved clinical data from

foreign sites. The FDA inspected only 1.9% of domestic trial sites and 0.7% of foreign trial sites in 2008.¹⁰⁰ Without conducting onsite inspections, the FDA cannot consistently and fully ensure that clinical investigators, sponsors, and independent review boards are adhering to the proper regulations while completing research.

In many instances, a failure to adhere to ethical guidelines coincides with the falsification of data. For example, in 1995, South African researcher and professor Werner Bezwoda conducted clinical trials to test a new treatment on women with Stage 4 (metastatic) breast cancer.¹⁰¹ In the 1999 meeting of the American Society of Clinical Oncology, he reported extremely favorable outcomes as a result of an expensive treatment of high-dose chemotherapy combined with bone marrow or stem cell transplants.¹⁰² When an on-site investigative team reviewed the trial data to verify Dr. Bezwoda’s findings, they found “substantial evidence of scientific misconduct.”¹⁰³ One-third of the trial subjects had not been officially enrolled and lacked any paperwork to verify their informed consent had been obtained or their eligibility to participate in the trial.¹⁰⁴ Many other patient files were incomplete or inconsistent with medical

⁹⁵ Ibid.

⁹⁶ Daniel Levinson. “The Food and Drug Administration’s Oversight of Clinical Trials.” Office of the Inspector General. 2007. <<http://oig.hhs.gov/oei/reports/oei-01-06-00160.pdf>>

⁹⁷ Levinson, “The FDA’s Oversight of Clinical Trials,” 5.

⁹⁸ Interagency collaboration, 21 U.S.C. § 393(c)(2009).

⁹⁹ Levinson, “The FDA’s Oversight of Clinical Trials.”

¹⁰⁰ Levinson, “The FDA’s Oversight of Clinical Trials,” ii.

¹⁰¹ Richard Horton. “After Bezwoda.” *The Lancet* 355 (2000): 942-943.

¹⁰² Christopher Weir and Gordon Murray. “Fraud in clinical trials: Detecting it and preventing it.” *The Royal Statistical Society*. December 2011.

¹⁰³ Raymond B. Weiss, Robert M. Rifkin, et al. “High-dose chemotherapy for high-risk primary breast cancer: an on-site review of the Bezwoda study.” *The Lancet* 355 (2000): 999-1003.

¹⁰⁴ Ibid.

records.¹⁰⁵ Furthermore, Dr. Bezwoda never submitted his research protocol to the sponsoring university's Committee for Research on Human Subjects for review, and failed to report three deaths that occurred as a result of his treatment. Before Dr. Bezwoda's findings were disproved, more than 30,000 American women opted for the procedure, which cost about \$100,000 per treatment.¹⁰⁶ Ten to twenty percent died after receiving the treatment, and the difference between the survival rates of those receiving the new therapy compared to the standard treatment was negligible.¹⁰⁷

The FDA's attempt to divert responsibility, by requiring that researchers abide by the clinical regulations of the host country, is as ineffective as asking them to use their own judgment in making ethical decisions. Before 2005, the majority of African countries had no mechanisms in place to regulate clinical research at all, and those that did gave no authority to any one agency to approve, inspect, or terminate clinical trials if deemed noncompliant with research standards.¹⁰⁸ In 2007, 116 researchers were interviewed who were conducting trials in Sudan; it was revealed that 53 of them were oblivious to the existence of governmental ethical committees, which

had been established in Sudan in 1979.¹⁰⁹

Because many African countries lack the infrastructure and resources to provide medical care to their citizens, in many cases the absence of regulation is deliberate. In efforts to supply their populations with health support and beneficial research, the governments of these nations often seek to attract pharmaceutical companies by stripping regulations and restrictions on research, or intentionally not enforcing them.¹¹⁰ Today, 40% or more clinical trials are taking place in Asia, Eastern Europe, and Latin America, where there are no required registry systems in place to keep track of the research conducted.¹¹¹ This makes it easy to exploit the lax regulation and minimal supervision. Research subjects from developing countries are also increasingly vulnerable due to the flexible informed consent guidelines of CIOMS, adjusted in an effort to cater to the communal realities that exist in parts of the developing world. Additionally, regional agreements fail to represent shared values and a streamlined system of regulation.¹¹²

In April 2008, the FDA announced that they would no longer require clinical research conducted

¹⁰⁵ Ibid.

¹⁰⁶ Thomas H. Maugh II and Rosie Mestel. "Key Breast Cancer Study Was a Fraud." *Los Angeles Times*. April 27, 2001.

¹⁰⁷ Susan Dentzer. "A Questionable Cure: Bone Marrow Transplants." *PBS*. May 13, 1999.

¹⁰⁸ D. Maiga, BD Akanmori, L. Chocarro. "Regulatory oversight of clinical trials in Africa: progress over the past 5 years." *Vaccine* 52.27 (2009): 7249-52.
<<http://www.ncbi.nlm.nih.gov/pubmed/19748580>>

¹⁰⁹ DE Elsayed and NE Kass. "Assessment of the ethical review process in Sudan." *Developing World Bioethics* 7.3 (2007): 143-8.

¹¹⁰ Benjamin Mason Meier. "International Protection of Persons Undergoing Medical Experimentation: Protecting the Right of Informed Consent." *Berkeley Journal of International Law* 513.20 (2002): 532-33.

¹¹¹ Keya Acharya. "India: Prime Destination for Unethical Clinical Trials." *Inter Press Service*. December 14, 2007.
<<http://www.commondreams.org/archive/2007/12/14/5838>>

¹¹² Meier, "International Protection of Persons Undergoing Medical Experimentation," 534.

abroad to comply with the Declaration of Helsinki. Rather, they must follow the Guideline for Good Clinical Practice, a standard “for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that the data and reported results are credible and accurate, and that the rights, safety, and well-being of trial subjects are protected.”¹¹³ The motives behind the shift were based on the idea that GCP provides more specific instructions and guidelines on how to responsibly monitor the trials and report harmful incidences, as well as ensures data quality and reliability by necessitating the submission of detailed information regarding adherence to protocol. Furthermore, since the Declaration of Helsinki is a document that is international by nature and privy to change independent of FDA authority, future revisions might conflict with U.S. laws and regulations, and GCP avoids this potential conflict.¹¹⁴

The FDA is the oldest, and one of the most powerful, regulatory agencies in the U.S., wielding authority over almost a quarter of Gross National Product and supervising more than one trillion dollars worth of consumer goods and one-third of all imported products.^{115,116} Considering the vast number of economic and political interests affected by the practices of the FDA, the degree to which

they may influence policymaking and regulatory decisions requires examination. Capture theory, a model put forth by Samuel Huntington (1952) and Marver Bernstein (1955) in the 1950s, suggests that older and established members of industry are better able to make political connections, and thus more capable of influencing regulations that benefit them and restrict smaller firms.¹¹⁷ The theory pertains to members of an industry sector whose dealings are affected by certain policy decisions, who then attempt to influence the process in pursuit of favorable policy outcomes. Regulatory capture occurs when these interest groups succeed in influencing public officials in “identifying with the interests of a client or industry.”¹¹⁸ There are two types of capture. The traditional form is “entry-barrier” capture, which strengthens regulation so that one section of industry is more privileged than the rest and market entry is more difficult. The other, more recently prevalent, form is called “corrosive” capture, which involves industry members pushing for deregulation and weaker enforcement.¹¹⁹

In recent years, industry capture

¹¹³ Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application. 21 C.F.R. § 312.120 (2008).

¹¹⁴

<http://www.regulations.gov/#!documentDetail;D=FDA-2004-N-0061-0002;oldLink=false>

¹¹⁵ Food and Drug Administration. “Operations in a Global Environment.” 2008.

¹¹⁶ Gardiner Harris. “The Safety Gap.” *The New York Times*. October 31, 2008.

¹¹⁷ Daniel P. Carpenter. “Protection without Capture: Product Approval by a Politically Responsive, Learning Regulator.” *American Political Science Review* 98.4 (2004): 613.

¹¹⁸ Gary Adams, Sharon Hayes, Stuart Weierner, John Boyd. “Regulatory Capture: Managing the Risk.” Australian Public Sector Anti-Corruption Conference. Sydney, 2007.

<http://www.iceaustralia.com/apsacc2011/pdf/papers07/day1_24oct07/StreamA2/RegulatoryCaptureManagingTheRisks_JohnBoyd.pdf>

¹¹⁹ Daniel P. Carpenter. “Corrosive Capture? The Dueling Forces of Autonomy and Industry Influence in FDA Pharmaceutical Regulation.” In Daniel Carpenter and David Moss (Eds.), *Preventing Capture: Special Interest Influence in Regulation, and How to Limit It*. The Tobin Project, 2011.

has shifted to the corrosive direction. In Washington, the eagerness to deregulate has resulted in lax consumer and environmental standards, freeing the private sector from government oversight of food safety, controls on greenhouse gas emissions, offshore drilling, and drinking water quality.^{120,121} Some argue that the promotion of the idea, “most regulation is unnecessary at best and downright harmful at worst,” has reinforced the public’s distrust of governmental involvement in industry, and delegitimized the idea of regulation itself.¹²² Dr. Marcia Angell, former editor-in-chief of the *New England Journal of Medicine*, wrote that the pharmaceutical industry specifically targets the FDA and exerts its influence by pushing legislation drafted by industry lobbyists, as well as through the administrative management of agencies “that are beholden to industry, and sometimes...openly hostile to the very idea of regulation.”¹²³ This has created a political environment in which agencies are pressured to cooperate with, rather than supervise, the industries they are obligated to regulate.

As recently as a couple of decades ago, pharmaceutical companies relied on academic researchers and physicians to

conduct clinical drug trials. This reliance was based on the pharmaceutical companies’ lack of expert staff and resources to design and execute the trials. Academic medical centers were able to supply their patients as research subjects, and the reputation of academic publications was needed to market the drugs.¹²⁴ But academic researchers, with many responsibilities (including teaching, research and patient care) in addition to clinical drug trials, found it increasingly difficult to carry out trials and produce medicines at the rate pharmaceutical companies wanted. Academic research offices and institutional review boards continued to delay the commencement of trials due to their slow review process of proposals. A drug manufacturer, on average, loses \$1.3 million every day a drug’s FDA approval is delayed.¹²⁵ Once the pharmaceutical industry found that it was more cost effective to employ their own research physicians to design and oversee clinical trials much faster, their reliance on academia decreased considerably.¹²⁶

Before 1980, the pharmaceutical industry had minimal influence on those who were recruited to research their products. Academic institutions that were paid to conduct studies had full responsibility and control over designing research procedure, analyzing and interpreting trial data, writing up results, and deciding where and how to report them. This allowed researchers and the institutions they worked for to have minimal ties to the companies that

¹²⁰ Jeffrey Smith. “A Last Push to Deregulate.” *The Washington Post*. October 31, 2008.

¹²¹ Dana Milbank. “Budget cuts as back-door regulation.” *The Washington Post*. April 2, 2012.

¹²² James Surowiecki. “The Regulation Crisis.” *The New Yorker*. 2010.

<http://www.newyorker.com/talk/financial/2010/06/14/100614ta_talk_surowiecki>

¹²³ Marcia Angell. “FDA: This Agency Can Be Dangerous.” Review of *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA*, by Daniel Carpenter. *The New York Review*, 2010.

<http://www.ahrp.org/cms/images/stories/articles/angell_fda_dangerous.pdf>

¹²⁴ Thomas Bodenheimer. “Uneasy Alliance—Clinical Investigators and the Pharmaceutical Industry.” *New England Journal of Medicine* 342 (2000): 1539-1544.

¹²⁵ Ibid, 1540.

¹²⁶ Ibid, 1540.

sponsored them. But recently, pharmaceutical sponsors have strengthened their authority and input regarding product research; they often design the studies, analyze the data, write the report, and decide how and where to publish them. Recent studies have demonstrated that the industry's increased influence on the research of its products has created conditions in which sponsors may alter or frame trial data in order to make them appear safer and more effective.¹²⁷ While academic researchers had minimal financial ties to their sponsors before, now they often "serve as paid consultants and members of speakers' bureaus and advisory boards and sometimes even have equity interest in the companies."¹²⁸ Another study demonstrated that approximately two-thirds of academic medical institutions hold equity interest in pharmaceutical companies that sponsor research in those institutions, two-thirds of medical school department chairs receive departmental income from drug companies, and three-fifths receive personal income from those companies.¹²⁹

In 1992, Congress passed the Prescription Drug User Fee Act (PDUFA), renewable every five years, which necessitates that pharmaceutical companies pay fees for regulation of their products. Companies pay around \$300,000 to apply for drug approval, an annual fee of \$145,000 for each manufacturing base, as well as a fee per product.¹³⁰ In return, the FDA must

adhere to stricter approval deadlines and improve responsiveness to companies during the drug development process. The new law was passed to help the FDA accelerate its costly monitoring and reviewing operations. In the late 1980s, drug approval times averaged at 30 months. In 1999, the median approval time was 11.6 months.¹³¹ Marcia Angell, in her article "Taking Back the FDA," criticizes the law, which she says "puts the FDA on the payroll of the industry it regulates... [And] makes it more likely that drugs will be reviewed favorably."¹³² Smaller pharmaceutical companies are put at a disadvantage; one British producer protested that the new user fees were even greater than revenue from U.S. markets.¹³³ Although user fees increased over the years, faster approval times are financially beneficial to the industry in the long run—"if you pay \$500,000 in user fees and get your [New Drug Application] approved one month earlier, you make more money... [It's] one of the few examples of paying the government an outrageous amount of money and you get back more than you pay."¹³⁴ In 2002, the FDA was estimated to receive \$162 million in user fees, which is nearly half the cost of reviewing drugs.¹³⁵ Because PDUFA is a renewable law and the FDA now relies so heavily on funding from

¹²⁷ Marcia Angell. "Industry-Sponsored Clinical Research: A Broken System." *JAMA* 300.9 (2008): 1069-1071.

¹²⁸ *Ibid*, 1070.

¹²⁹ *Ibid*, 1070.

¹³⁰ Ray Moynihan. "Science, industry, and politics at the FDA." *British Medical Journal* 327.160

(2003).

¹³¹ Public Citizen. "Problems in the New Drug Approval Process: A Case Study of Lotronex." 2010.

<http://www.citizen.org/congress/article_redirect.cfm?ID=7442>

¹³² Marcia Angell. "Taking Back the FDA." *The Boston Globe*. February 26, 2007.

¹³³ Fran Hawthorne. *Inside the FDA: The Business and Politics Behind the Drugs We Take and the Food We Eat*. John Wiley & Sons. (2005): 152.

¹³⁴ *Ibid*, 152.

¹³⁵ Moynihan, "Science, industry, and politics at the FDA."

pharmaceutical companies, industry is in a prime negotiating position and can threaten to challenge the PDUFA renewal and withdraw funding.

David Williams, in his 2001 Pulitzer Prize-winning *Los Angeles Times* article, revealed that the FDA was mounting enormous pressure on its drug reviewers to work more quickly. An anonymous pharmacologist working in the FDA's scientific investigations division admitted, "the devil is in the details, and detail is something we no longer have the time to go into."¹³⁶ William Schultz, the FDA deputy commissioner from 1995-1999, explained: "You can meet the goal by either approving the drug or denying the approval. But there are some who argue that what Congress really wanted was not just decisions, but approvals. That is what really gets dangerous."¹³⁷ Kathleen Holcombe, a former FDA legislative affairs staffer and congressional aide, pointed out that while historically, the FDA operated according to the motto, "Regulate, be tough, enforce the law, and don't let one thing go wrong," the FDA more recently "sees itself much more in a cooperative role" with the pharmaceutical industry.¹³⁸

In 1998, Public Citizen, a nonprofit, consumer rights advocacy group, surveyed FDA Medical Officers in charge of reviewing drug applications and found that out of the fifty-three who responded to the survey, nineteen officers recalled twenty-seven market-approved drugs

they believed should not have been approved. A study done in 2005, by Edmund Pezalla, revealed that that more than 51% of market-approved drugs may have had severe adverse effects that went undetected before approval.¹³⁹ In 2009, the FDA recalled 1,742 prescription medications from the market, growing 309% from just 426 in 2008.¹⁴⁰

Most criticism directed at the FDA rests on its perceived inability to efficiently respond to the safety concerns surrounding already approved drugs and their failure in post marketing safety surveillance. This is perhaps due to the FDA's lack of "clear and effective processes for making decisions about, and providing management oversight of, post market safety issues."¹⁴¹ Dr. David Graham, an epidemiologist working as the Associate Director of the FDA's Office of Drug Safety, condemned the FDA for dealing with safety concerns in a perverse way that makes consumer welfare a peripheral responsibility. He wrote that the FDA refuses to act on safety concerns and alarming evidence during the preapproval process that may point to potential complications unless there is "complete certainty" of an increased risk due to the medication. This practice fails to protect consumers, is partial to industry interests, "rewards drug companies for not aggressively pursuing safety questions, and guarantees that

¹³⁶ David Willman. "How a New Policy Led to Seven Deadly Drugs." *Los Angeles Times*. December 20, 2000.

<<http://www.latimes.com/news/nationworld/nation/la-122001fda,0,4840718,full.story>>

¹³⁷ Ibid.

¹³⁸ Ibid.

¹³⁹ Edmund Pezalla. "Preventing adverse drug reactions in the general population." *Managed Care Interface* 18.10 (2005): 49-52.

¹⁴⁰ Parija Kavilanz. "Drug Recalls Surge." *CNN Money*. August 2010.

¹⁴¹ BM Psaty, SP Burke. "Protecting the health of the public: Institute of Medicine recommendation on drug safety." *New England Journal of Medicine* 355.17 (2006): 1753-5.

<<http://www.ncbi.nlm.nih.gov/pubmed/17030843>>

some drugs with major safety problems will be approved, and, once approved, will remain on the market, even in the face of extensive patient harm.”¹⁴² This serves as evidence that the FDA is more interested in getting drugs on the market, rather than thoroughly evaluating the drugs, especially once they have already been market-approved.¹⁴³

In a report prepared for Rep. Henry Waxman in 2006 by the Committee on Government Reform, the FDA’s enforcement record was examined over the course of a 15-month investigation. The Committee reported that FDA enforcement in every sector had declined by over 50% since 2000, during the Bush Administration.¹⁴⁴ The FDA issued 50% less warning letters for regulation infringements, and confiscated 44% less mislabeled, defective, or dangerous products. Furthermore, FDA officials failed to act on the recommendations of agency field inspectors reporting violations in 138 cases. The report also mentioned the decline in FDA enforcement was not a result of manufacturers’ increased level of adherence to regulation, and that FDA field inspectors found no decrease in

violations from years before.¹⁴⁵ In response to these statistics, Dr. Jerry Avorn, an expert consultant, characterized the FDA as “an agency unwilling to exert its regulatory authority in defense of the public’s health.”¹⁴⁶ The only measure of FDA enforcement that increased in the five-year span was the number of drug recalls. In 2000, 3,716 FDA-regulated drugs were recalled. In 2005, the number of recalls increased by 44%, to 5,338.¹⁴⁷ This increase indicates the FDA’s serious neglect of adequate pre-approval measures.

Dr. Sidney Wolfe, Director of Public Citizen’s Health Research Group for more than thirty years, laments the unprecedented rise of health complications and deaths due to unsafe prescription drugs, emphasizing the number of clear warning signs that surface before and immediately after unsafe drugs come on the market. “In all cases, once they came on the market, there was a very dangerous and reckless slowness to respond to the signals that came after marketing.”¹⁴⁸ The failures of the pre-approval phase as well as of the post-market safety surveillance phase contribute to delays in pulling drugs off the market – delays that cost thousands of lives. The U.S., compared to other first world countries like France and the United Kingdom, has an ineffective system of reporting adverse events of prescription drugs. Dr. Wolfe approximates that only between 1-10% of adverse reactions from prescription

¹⁴² Russell G. Thornton. “Preemption, tort reform, and pharmaceutical claims.” *Baylor University Medical Center* 21.1 (2008): 82-92. <<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2190559/>>

¹⁴³ Jerry Avorn. “Paying for Drug Approvals – Who’s Using Whom?” *New England Journal of Medicine* 356 (2007): 1697-1700. <<http://www.nejm.org/doi/full/10.1056/NEJMp078041>>

¹⁴⁴ Committee on Government Reform, Special Investigations Division. “Prescription for Harm: The Decline in FDA Enforcement Activity.” June 2006. <<http://oversight-archive.waxman.house.gov/documents/20060627101434-98349.pdf>>

¹⁴⁵ *Ibid*, i.

¹⁴⁶ Letter from Dr. Jerry Avorn to Representative Henry A. Waxman (May 25, 2006).

¹⁴⁷ Committee on Government Reform, Special Investigations Division, “Prescription for Harm: The Decline in FDA Enforcement Activity,” 9.

¹⁴⁸ Sidney Wolfe interview.

drugs are reported to the FDA. This increases the time it takes to pull the drug from the market or enforce a black box warning.¹⁴⁹ Dr. Wolfe goes on to claim that post-market surveillance analyses are often received poorly or with hostility by FDA officials, who “are wedded to the idea that when they approved the drug, it must have been OK or we wouldn’t have approved it... [They] tend to take very, very negatively the criticism that comes from those people that do post-market surveillance.”¹⁵⁰

Jim Dickinson, an established columnist and the editor of *FDA Review*, has tracked FDA policy developments and deregulatory shifts for the past three decades, wrote in 2010:

“It has taken almost a generation, but by now, the pro-industry infiltration of FDA’s culture is firmly entrenched. Not only is collaboration in product reviews officially encouraged, but good relationships across the regulatory fence hold the prospect of a possible future career in a well-paid industry job – a connection that is less likely to be publicly noticed in news media that now have to line up for information that has been filtered through agency press offices. The arm’s-length relationship that formerly ruled every contact between agency and industry has become a

fading memory.”¹⁵¹

The FDA and pharmaceutical industry collaborate in other harmful ways – a phenomenon dubbed “the revolving door,” which occurs in every regulatory agency and level of government. Many FDA employees find themselves working as consultants for pharmaceutical companies after their stint at the agency.¹⁵² This is a concern especially when drug reviewers, still employed by the FDA, but looking to apply for jobs at large pharmaceutical companies in the near future, are hesitant to give unfavorable reviews. The Center for Responsive Politics published a report in 2006 listing fifty-three individuals who at one time worked for various government agencies, and had either before or afterwards worked for a private sector employer in the health industry.¹⁵³ Billy Tauzin, a member of the House of Representatives (1980-2005) and the Chairman of the House Energy & Commerce Committee, which was highly influential in drafting the Medicare drug benefit, went on to become the President of the Pharmaceutical Research and Manufacturers of America (PhRMA) in 2005.¹⁵⁴ Michael Friedman, the Acting Commissioner of the FDA (1997-1998),

¹⁵¹ Merrill Goozner. “FDA More Pro Industry than Any Time in 35 Years.” The Health Care Blog. January 16, 2010.

¹⁵² Hawthorne, *Inside the FDA: The Business and Politics Behind the Drugs We Take and the Food We Eat*, 150.

¹⁵³ Consumer Project on Technology. “Revolving door between the U.S. Government and Industry.” February, 2006.
<<http://www.cptech.org/ip/health/politics/revolvingdoor.html>>

¹⁵⁴ William M. Welch. “Tauzin switches sides from drug industry overseer to lobbyist.” *USA Today*. December 15, 2004.
<http://www.usatoday.com/money/industries/health/drugs/2004-12-15-drugs-usat_x.htm>

¹⁴⁹ Ibid.

¹⁵⁰ Ibid.

later became the Senior Vice President of the Pharmacia Corporation, and PhRMA's Chief Medical Officer for Biomedical Preparedness.¹⁵⁵ Gerald J. Mossinghoff, the former Assistant Secretary of Commerce and Commissioner of Patents and Trademarks from 1981-1985, became a registered lobbyist for PhRMA in 1998. Susan K. Finston, who formerly worked at the State Department in the Office of Intellectual Property and Competition, now works as the Assistant Vice President for Intellectual Property and Middle East/African Affairs at PhRMA. Edward Allera, the Associate Chief Counsel for Enforcement at the FDA from 1974-1978, later became a partner at a law firm with clientele including Pfizer and PhRMA, and a lobbyist for Johnson & Johnson in 1998. These are only a few examples of high-level state officials who later would go on to work for the very industry they worked for years to regulate.

Daniel Carpenter, a professor of government at Harvard, published a study in 2002 in which he reviewed 450 drugs approved by the FDA between 1977 and 2000. He concluded that the most prominent sources of influence were "the number of times a disease was mentioned in *The Washington Post*, the budget of the Center for Drugs, and the budgets of patient advocacy groups."¹⁵⁶ In other words, FDA approval rates are spurred by public pressure and available resources. Although Carpenter's study did not look at industry influence, he admitted, "Firm attributes undoubtedly sway the FDA's decision making in drug approval

cases."¹⁵⁷ Also, the pharmaceutical industry is known to make direct contributions and giving support to patient advocacy groups, which are often the parties that attract media attention.

Carpenter also studied the bias against small companies that permeates the approval process. It is an accepted fact that large, established companies face fewer obstacles in obtaining drug approval. Carpenter studied 766 drugs submitted between 1979 and 2000, and analyzed review times, political contributions from companies, the ownership of companies, and the budgets of patient advocacy groups. He found that large companies often complete the approval process much faster. After a 15-month review process, more than 40% of products submitted by large companies were approved while only 15% of products from small companies were given approval. He attributed this to "the greater regulator familiarity that large firms enjoy," explaining that having a prior relationship with the agency can result in a 55% advantage in approval times.¹⁵⁸

To illustrate how the FDA appeases the pharmaceutical industry in regulatory practice, I will take closer look at the development, approval process, and post marketing surveillance measures of a drug called Lotronex. This case study epitomizes the FDA's heavy reluctance to act on the recommendations of its drug reviewers and in the best interest of the consumer population,

¹⁵⁵ "Michael A. Friedman: Profile." *Forbes*. <<http://people.forbes.com/profile/michael-a-friedman/68507>>

¹⁵⁶ Hawthorne, *Inside the FDA*, 154.

¹⁵⁷ Ibid, 158.

¹⁵⁸ Daniel Carpenter, Brian Feinstein, Colin Moore, et al. "Why Do Bigger Firms Receive Faster Drug Approvals?" *Harvard Medical School*. (2004): 29. <<http://people.hmdc.harvard.edu/~dcarpent/whybigfast1.pdf>>

prioritizing industry interests over safety concerns.

In July 1999, GlaxoWellcome (now GlaxoSmithKline) submitted a New Drug Application for Alosetron (Lotronex), a drug developed to treat irritable bowel syndrome in women. Irritable bowel syndrome is not a fatal condition, but Lotronex was given an accelerated review. Although 27% of the women in the clinical trial experienced constipation and 10% had to withdraw from the study, Glaxo labeled constipation an “infrequent side effect,” even though constipation can cause severe complications in women with IBS.¹⁵⁹ The medical officer reviewing the drug noticed that there were four cases of ischemic colitis, a serious and rare condition, which occurred in the experimental group during the trials.¹⁶⁰ The review noted that this “[represents] a signal of a potentially serious problem that should be anticipated, perhaps even more severely expressed, if the drug is approved for clinical use.”¹⁶¹ Despite the fact that only 10-20% of trial subjects reported improvement due to Lotronex and women in one trial group reported a level of relief between 0.12-0.14 (on a scale of 0-4) higher than women in the

placebo group, the drug was approved in February of 2000.^{162,163} Less than two months later, a multitude of adverse events were reported, including eight cases of ischemic colitis and six hospitalizations.¹⁶⁴ The FDA reconvened to review its decision, attempting to label Lotronex with a black box warning. Glaxo protested, and they agreed instead to include a Medication Guide with each prescription to describe symptoms of dangerous side effects.¹⁶⁵ But by November, five patients were dead and there were many more reports of adverse effects.¹⁶⁶

In November 2000, FDA Medical Officers rejected Glaxo’s risk management proposals and insisted, “the sponsor has not identified a subset of women who will respond to Lotronex therapy safety... a risk management plan cannot be successful that will eliminate deaths, colectomies, ischemic colitis, and complications of treatment that were never seen previously in the management

¹⁵⁹ Sidney Wolfe, M.D., Director of Public Citizen’s Health Research Group, in testimony before the U.S. Food & Drug Administration’s Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Subcommittee of the Advisory Committee for Pharmaceutical Science, April 23, 2002.

¹⁶⁰ Public Citizen’s Health Research Group, “Petition to the Food and Drug Administration to remove Lotronex from the market,” Publication #1533; August 31, 2000.

¹⁶¹ John R. Senior, M.D., “FDA Medical Review: Lotronex, NDA 21-107, 90-Day Safety Update” November 30, 1999, p. 22.

¹⁶² Joseph Shapiro, “A pill turned bitter: How a quest for a blockbuster drug went fatally wrong,” *U.S. News & World Report*, Vol. 129, Issue: 23: December 11, 2000.

¹⁶³ Public Citizen’s Health Research Group, “Petition to the Food and Drug Administration to remove Lotronex from the market,” Publication #1533; August 31, 2000.

¹⁶⁴ Ibid.

¹⁶⁵ Ibid.

¹⁶⁶ Department of Health and Human Services. Lotronex (alosetron) safety and risk management summary. Memorandum PID [D000674, 16 November 2000. <www.citizen.org/documents/1566.pdf>

of IBS.”¹⁶⁷ Despite this, the FDA proposed the “restricted distribution” of Lotronex, although Glaxo opted to pull Lotronex from the market, having already made \$56 million off the drug.¹⁶⁸

In response to a public outcry and patients’ willingness to accept the risks associated with Lotronex, Glaxo applied to re-market the drug in December of 2001. Although safety reviewers emphasized, “potentially everyone who takes Lotronex is at risk,” the FDA advisory committee reapproved the drug in 2002, under the condition that the dosage would be halved and restricted to patients who had exhausted traditional forms of treatment.¹⁶⁹ As a result of his experience, Dr. Paul Stolley, who joined the FDA in 2000 as a senior consultant assigned to examine the post marketing safety of Lotronex, went on to become a contributing staff member at Public Citizen, a consumer advocacy group. He spoke out against the FDA, which he called “a servant of industry,” after the re-approval of Lotronex: “I think it’s a shame how it has fallen down on the job, and Lotronex is a perfect example. The FDA

¹⁶⁷ Kathleen Uhl, Zili Li, Ann Corken Mackey, and Paul Stolley. “Lotronex Safety & Risk Management Summary.” FDA. Center for Drug Evaluation and Research. April 23, 2002.

<http://www.fda.gov/ohrms/dockets/ac/02/briefing/3848B1_02_FDA%20Lotronex.pdf>

¹⁶⁸ U.S. Food and Drug Administration, “Glaxo Wellcome Decides to Withdraw Lotronex from the Market,” Talk paper: T00-65; November 28, 2000.

¹⁶⁹ Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Subcommittee of the Advisory Committee for Pharmaceutical Science, 23 April 2002.

<www.fda.gov/ohrms/dockets/ac/02/transcripts/3848T1.pdf>

was in partnership with industry. It should have been negotiating, not in partnership. Why was it in partnership? Because it’s financially supported by industry.”¹⁷⁰

CONCLUSIONS

The era of globalization has facilitated the emergence of a new set of global health problems that challenge the traditionally unilateral and domestic approaches of state efforts. Regulatory agencies like the FDA are no longer able to fully address the public health threats that endanger their populations or the jurisdictional limitations that hinder their regulatory authority. The globalization of clinical research necessitates an expansion of ethical oversight. International codes of conduct contribute important substantive standards, but lack legal enforcement mechanisms, and fail to be widely implemented due to the absence of competent regulatory agencies in many parts of the developing world. The FDA has enormous potential to protect research subjects and enforce ethical standards due to its position as the gatekeeper to the most profitable market for prescription drugs in the world. In 2005, the U.S. spent more on prescription drugs than Australia, Canada, Germany, Netherlands, New Zealand, and the United Kingdom combined.¹⁷¹ With this level of influence, any improvement in the FDA’s regulatory efficacy would be valuable in

¹⁷⁰ Ray Moynihan. “Alosetron: a case study in regulatory capture, or a victory for patients’ rights?” *British Medical Journal* 325 (2002): 592-595.

<<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1124108/pdf/592.pdf>>

¹⁷¹ S. Morgan and J. Kennedy, Prescription Drug Accessibility and Affordability in the United States and Abroad, The Commonwealth Fund, June 2010.

ensuring ethical and technical clinical compliance internationally.

But as much as agency capacity is limited by resources, international collaboration, and jurisdictional limitations, it is even more profoundly debilitated by industry interests. As I have demonstrated, FDA control has been gutted by a complex process of industry capture. In a political climate brimming with anti-regulatory opinion, conflicts of interest are becoming more and more embedded into agency structure: the revolving door between industry and agency, and the Prescription Drug User Fee Act increasingly put regulators at odds with their duties. In order to pursue the expansion of regulatory oversight both domestically and abroad, industry influence must be limited. To prevent the occurrence of the revolving door paradigm, stringent conflict of interest laws must be implemented to restrict former high-ranking FDA officials from becoming pharmaceutical company board members. In the interest of consumer safety, the FDA should enforce and enhance post market safety surveillance, and expedite drug recalls when significant reports of adverse effects first emerge. Continued apathetic inaction regarding the industry's influence on pharmaceutical regulation is a gross disregard for consumer safety and research subject welfare.

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